To Prof. Lian-Sheng Ma. Founder and CEO

and Jin-Lei Wang. Company Editor-in-Chief

World Journal of Clinical Cases

BPG Editorial Office

Title: "Correlation between betatrophin/angiogenin-likeprotein3 /lipoprotein lipase pathway and severity of coronary artery disease in Kazakh patients with coronary heart disease" (Manuscript No.: 71063).

Dear Prof. Lian-Sheng Ma and Jin-Lei Wang,

On behalf of all the contributing authors, I would like to express our sincere appreciations of your letter and reviewers' constructive comments. All the authors have seriously discussed about all these comments. According to the reviewers' comments, we have tried best to modify our manuscript to meet with the requirements of your journal. In this revised version, changes to our manuscript within the document were all highlighted by using yellow colored text. Point-by-point responses to the reviewers are listed below this letter.

(1) We have revised the P-values in the summary and results sections in the manuscript.

(2) We have revised the discussion in the manuscript. The results have been compared with the available literature, and comments have been made.

(3) We have already updated the references.

(4) All the figures were originally prepared by the authors, and the original power point file were submitted.

(5) The titles of the tables have been revised, and abbreviations were added below the tables.

(6) We have explained the clinical relevance of this study.

(7) We have added some discussions on the implications of the research results for coronary heart disease management strategies, and combined the findings of this study and its clinical application to provide some insights.

Thank you very much for your time and consideration.

Respectfully,

Xiang Ma, M.D., Ph.D.

Department of Cardiology

The First Affiliated Hospital of Xin jiang Medical University

Urumqi 830054, China

Tel: +86-13669939349

Email: maxiangxj@yeah. net

Point by point response:

1. The P-values are not correctly presented. Write P<something only if P<0.001. If P is between 0.001 and 0.05 write the exact P-value. Please correct the results section.

Response: Thank you so much for pointing out this error. We have revised the incorrectly presented P-values of the abstract and results in the manuscript, and the changes in the manuscript are highlighted in yellow text.

2. The discussions can be improved, you need to compare your results with the available literature and comment on them, not just review the literature.

Response: Thank you very much for your kind comments on the discussion section of our manuscript. In the discussion section, we have added a comparison of the differences between the results of this study and those in the available literature. Based on the knowledge of betatrophin, angiogenin-likeprotein3, and lipoprotein lipase, we also analyzed the reasons for these differences. Changes that have been revised in the discussion section of the manuscript are highlighted in yellow text.

3. Maybe the authors can add newer references too, only 11/31 are from 2018 onwards.

Response: Thank you very much for your suggestions. These suggestions are all valuable and helpful for improving our article. We have updated the reference list as per journal requirements in the revised manuscript. The

updated reference numbers are: 2, 3, 5, 8-13, 15, 18, 21-22, 25-28, and 30. We have highlighted updates to references in the revised manuscript in yellow text

4. Are the figures originally prepared by the authors?

Response: We thank the reviewers for their kind reminders of the source of the figures in our manuscript. All the figures were originally prepared by the authors, and the original power point file were submitted.

5. What is the clinical relevance of your study?

Response: We are very grateful to the reviewers for their attention to the clinical relevance of this study. We believe that the clinical relevance of this study has the following points: (1) Previous studies have presented different views on the relationship and interaction mechanism between betatrophin, angiopoietin-like protein 3, and lipoprotein lipase. Therefore, we conducted a retrospective study in Chinese coronary heart disease patients, and the results of this study show that this pathway is correlated with the severity of coronary artery disease. (2) When the coronary artery disease is aggravated, the increase of the expression level of betatrophin/angiogenin-likeprotein3/lipoprotein lipase pathway may provide clues for the diagnosis of coronary heart disease. Therefore, the detection of the expression level of this pathway may be used in clinical practice as a non-invasive detection method for coronary heart disease diagnosis. (3) The results of this study show that the level of betatrophin in coronary heart disease patients is increased, and it is consistent with the changes in the level of angiogenin-likeprotein3. Betatrophin and angiogenin-likeprotein3 may jointly participate in the lipid regulation of coronary atherosclerosis, and it may become the next target of lipid regulation therapy for coronary heart disease patients.

6. What strategies do you propose based on your findings for a better management of CHD patients? How can you translate your results from the bench to the bedside?

Response: We feel great thanks for your professional review work on our article. Based on our findings, the recommended management strategies for CHD patients are as follows: (1) The detection of betatrophin, angiogenin-like protein 3, and lipoprotein expression levels may be used in clinical practice as one of the assessment tools for the severity of coronary artery disease in CHD patients. (2) Previous studies have confirmed that inhibiting the activity of angiogenin-likeprotein3 can effectively achieve lipid regulation, betatrophin can be used as a new therapeutic target in lipid regulation to improve the management of blood lipids in patients with CHD. (3) Logistic regression analysis revealed that betatrophin, triglycerides, and body mass index are risk factors for coronary heart disease. Therefore, the improvement of these factors will bring benefits to the management of patients with coronary heart disease. According to our results, three relevant aspects of the clinical application can be derived from the study: (1) The detection of betatrophin, angiogenin-like protein3, and lipoprotein lipase can provide diagnostic clues in the assessment of the severity of coronary artery disease in CHD patients. (2) The development and application of related drugs that use betatrophin as a therapeutic target may improve the management of blood lipid levels and reduce the risk of CHD.

(3) Effective management of triglyceride levels and body mass index in CHD patients can reduce the risk of cardiovascular events.